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Discussion by H. Z. LUND, Western Reserve University, Cleveland, O.

From the standpoint of the surgical pathologist, recognition of early melanoblastoma and distinction from benign nevus are extremely important. The first feature which is looked for is junctional proliferation because most, if not all, melanoblastomas arise in the epidermis or at the dermo-epidermal junction. Traub and Keil have stressed this and awakened many to awareness of it. However, the emphasis has been insufficiently critical and there has been an acceptance by some dermatologists and pathologists that the presence of junctional proliferation at any age and of any degree is evidence of a potentially malignant lesion. Such a conclusion is drawn from the article by Traub and Keil. Actually the feature of junctional proliferation becomes significant if it is unusual in degree for a given age, as, for example, the finding of a nevus of a middle-aged person which has the histological characteristics of a nevus of childhood; i.e., the cells are largely junctional in distribution, resemble epithelium and there is little evidence of differentiation to ordinary nevus cells and cells associated with fibrils. Such an appearance leads to the suspicion that the lesion is incipient and growing. (The clinical evidence obtained in our own analysis of the duration of growth of such lesions was variable and conflicting, permitting no final conclusion. Additional study is needed.) The pathologist is to be guarded in excluding melanoblastoma in these cases, but until more conclusive evidence is obtained, a positive diagnosis must rest on this finding plus additional changes, including (a) excessively large, irregularly scattered or otherwise bizarre masses or nests of cells at the dermo-epidermal junction, (b) deep penetration of large cells without differentiation to small nevus cells and fibrillar forms, (c) more mitotic figures than are usual, (d) atypical and pleomorphic cells, (e) invasion, (f) trophic changes, and (g) inflammation. other than folliculitis, which is not accounted for by trauma.

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Discussion by S. WILLIAM BECKER, University of Chicago School of Medicine.

The term "junction nevus" has been criticized because such designation includes both "A" and "AB" nevi, for which it could be legitimately used, and, in addition, the obligative premalignant (or actually malignant, depending on the criteria used) disorder called "lentigo maligna" by Dubreuilh. My preference is to designate as pigmented nevi only those lesions composed of benign melanoblastic cells (nevus cells).

Dr. Traub has again emphasized the necessity for microscopic examination of nevi and tumors with which they may be confused. He has shown with excellent colored photographs, a "junction nevus" and an "intraepidermal nevus" which cannot be distinguished clinically. On the basis of his excellent colored photomicrographic slides of the two disorders, it would seem that the first satisfies fully all the requirements of "lentigo maligna" of Dubreuilh. The second is composed entirely of epithelial cells and contains no neoplastic melanoblasts, and would seem to belong in the group of benign epidermal neoplasms (Becker, S. W.: Benign Epidermal Neoplasms, Arch. Dermat. and Syph., 26:838 (Nov.) 1932) and could be called "benign epithelioma."

At any rate, it seems more scientific to classify pathologically rather than to perpetuate the older designation "nevus" in the sense of a "mark."

The Development of Epidermal Pigmentation in the Negro Fetus.

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Fetal Negro skin constitutes excellent material for the study of melanogenesis. Surprisingly, no systematic survey, throughout the fetal stages, had previously been made. The main advantages reside primarily in the high potentiality for melanin production of specialized cells which reveal their activity early in fetal life. They are the dendritic melanoblasts which remain distinct, both morphologically and functionally, from ordinary epithelial cells. They are the sole producers of melanin both in the epidermis and in the papillae of hair follicles. The distribution and signficance of dendritic cells in the adult human skin, both white and pigmented, recently was studied by Billingham.

The derivation of mammalian melanoblasts from the neural crest has been demonstrated by Rawles (1947). In the fetal Negro

skin, however, the search for migratory melanoblasts in the dermis, previous to their identification in the epidermis, encounters difficulties. If potential melanoblasts are present in the embryonic or early fetal dermis they cannot be demonstrated either by a positive dopa-reaction or by the usual silver techniques. This might be due to insufficient amounts of a melanogenous substrate (tyrosine) or to incomplete, as yet inactivated oxidizing enzyme-systems in the precursors of epidermal melanoblasts. The latter assumption appears more probable. Experimental evidence in Amphibia has established the fact that the ectoderm plays an important role in melanin formation (DuShane, 1943). My observations in the fetal Negro skin, so far, appear to confirm the hypothesis that substances necessary for the synthesis of melanin may be supplied by epidermal cells. An appositional relationship of human melanoblasts to the epidermis seems to be essential for their full functional activity. The material for this histological study of fetal Negro skin consisted of skin-specimens from 75 abortions. The main results may be summarized as follows:

1. The basal cells of the human epidermis do not produce melanin.

2. The true source of melanin resides solely in the pigmentary dendritic cells or melanoblasts which constitute an independent cell-type within the epidermis.

3. Dendritic melanoblasts first appear in the fetal Negro skin early in the third month.

4. There are no cytological or functional transitions between epidermal melanoblasts and ordinary epithelial cells.

5. The dendritic melanoblasts consistently show a positive dopa-reaction throughout fetal life. Basal and other epidermal cells remain dopa-negative.

6. Dendritic melanoblasts of the third fetal month contain melanin-precursors (premelanin) which can be demonstrated by reduced silver methods. From the fourth fetal month to term they contain both premelanin and melanin granules.

7. The earliest melanoblasts in the epidermis have ovoid, fusiform or stellate cell-bodies with few and short dendritic processes at their poles. In the fourth fetal month the total length of dendritic melanoblasts may reach 100 microns. Their primary dendritic processes extend through the epidermal intercellular spaces and begin to form an intricate syncytium.

8. During the fifth fetal month numerous secondary dendritic processes arise from the long primary processes of the melanoblasts. These secondary tufts approach and progressively surround the ordinary epithelial cells mainly on their distal pole.

9. In unstained sections, brown melanin granules are first identified within the melanoblasts in the late fourth and early fifth fetal months.

10. The transfer of melanin granules elaborated in the dendritic melanoblasts to neighboring epithelial cells begins late in the fifth fetal month. This process is accentuated throughout the remainder of the fetal period. The transfer occurs mainly from the secondary dendritic processes and leads to the accumulation of melanin in ordinary epidermal cells as "supra-nuclear caps." The active melanoblasts gradually become concealed among the pigment-carrying epithelial cells.

11. Melanization of hair shafts and of the matrix of the papillae in all essentials is similar to that of the epidermis. Dendritic melanoblasts accumulate in the papillae and extend their processes directly into the growing base of hair-shafts, thus melanizing them independently of a pigmented epithelial matrix. The latter receives melanin granules quite secondarily after melanization of the hair shaft is well under way.

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Discussion by HERMANN PINKUS, Wayne University Medical College, Detroit, Mich.

Dr. Zimmermann in his splendid investigation was unable to find evidence of multiplication of fetal melanoblasts. Masson (The Biology of Melanomas, 1948, p. 31 and plate 15, fig. 1) has stated his belief that epidermal melanoblasts usually multiply by amitosis, but says that he saw one unquestionable mitosis. I would like to contribute the purely accidental observation of mitotic division of normal dendritic pigment cells in the basal layer of adult human skin. (Pinkus, H.: Mitotic Division of Human Dendritic Melanoblasts, *J. Investig. Dermat.*, 13: 309-311, Dec., 1949). The specimen was a common wart (verruca vulgaris) taken from the finger of a dark colored woman. Two unquestionable and two suggestive instances of mitosis were seen in twenty-four routine histologic sections. Mitosis of Malpighian cells was common in this specimen. Without doing an actual count, it was my impression that the ratio of dividing and resting nuclei was similar for dendritic and Malpighian cells.

This experience proves that human melanoblasts can multiply by mitosis in non-malignant conditions. I have also recently observed occasional instances of mitosis of benign nevus cells in ordinary papillomatous nevi.

A Comparative Study of Malignant Melanoma Among Negro and White Patients.

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The admissions to Charity Hospital of Louisiana at New Orleans are nearly equal for white and Negro males and females. During the period from 1937 to date, there have been 101 cases of malignant melanoma among 26,800 malignant tumors in 686,293 admissions. That is, approximately 4 cases of malignant melanoma occurred per 1,000 cases of malignancy.

Approximately one-third (32%) of these melanomas occurred in Negro and two-thirds in white patients. The sex incidence in the Negro group was equal, whereas the incidence in white females was slightly higher than in white males. The majority of cases (88%) occurred between the ages of 30 and 80 years, those in Negroes having highest incidence some ten years later than those in white persons.

The foot was the most common site for the primary lesion in the Negro (50%) while in the white race the trunk was most common (33%). A pre-existing mole was described in one-third of the cases, mostly white. A history of trauma was elicited in one-half of the Negroes and one-tenth of the white patients. It is not possible to tell how much of the trauma was coincidental and falls in the *post hoc, ergo propter hoc* class. Clinical evidence of regional lymph node metastasis was found in about one-half of the cases. Better results of therapy were obtained when it was administered in the hospital rather than as hospital outpatients or in a physician's office and when the metastases as well as the primary lesions were included in the plan of treatment. Inadequate excision with recurrence of the primary lesion was recorded in 17 cases. Two cases of melanoma appearing during pregnancy were found to be of anaplastic histological appearance and were fatally terminated in a short time. The mean duration of life was 4 years and 5 months for the entire group. Eighteen out of 42 patients had a family history of at least one other individual with cancer. None of these had melanoma, however.

The sex incidence of malignant melanomas found is in agreement with that reported by Pack and co-workers (8) in an analysis of 862 cases. Dawson also found a history of the presence of a mole in one-third of the cases. However Pack et al (8) and Broders and MacCarthy (4) record this finding in one-half of their cases. Perhaps this discrepancy may be explained by the low incidence of antecedent moles among Negroes. The incidence of concomitant trauma is similar to that given by Pack et al (8) but much lower than that given by Horwitz (5), 57%. The tumor may arise from any portion of the Negro's skin or eye as Sutton and Mallia (10) have reported. However, when the lesion occurs, it is more apt to arise in the less pigmented areas of the body, such as the foot (7). The individuals in which they appeared were not all lightly pigmented but in many instances were exceedingly dark. The rapidity of the process in two Negro males followed to termination demonstrates that de Lignis' (6) conclusion that malignant melanoma in the native of Northern Transvaal is a less intense process does not always hold true for the Negro in America. The evidence given here would indicate that the American Negro is not as peculiarly immune to malignant melanoma as one might assume from the literature. (1, 2, 3).

SUMMARY.

1. Malignant melanoma was approximately one-half as frequent in Negroes as in white persons in a population of patients equally divided as to race and sex. This is a higher incidence than that usually quoted for Negroes.

2. Malignant melanomas arose more frequently from a mole in white than in Negro patients.

3. Metastases to regional lymph nodes occurred frequently.

4. Early therapy is better performed by those capable of treating not only the primary but also secondary lesion.

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